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(54) **Title:** THIENODIBENZOAZULENE COMPOUNDS AS TUMOR NECROSIS FACTOR INHIBITORS

(57) **Abstract:** The present invention relates to the dibenzoazulene compounds represented by formula I as well as to their pharmaceutical preparations for the inhibition of tumor necrosis factor alpha (TNF α) and interleukine 1 (IL-1) in mammals at all diseases and conditions where these mediators are excessively secreted. The compounds of the present invention also demonstrate an analgetic action and can be used to relieve pain.

THIENODIBENZOAZULENE COMPOUNDS AS TUMOR NECROSIS FACTOR INHIBITORS

Technical Field

The present invention relates to new derivatives of 1-thiadibenzoazulene, their pharmacologically acceptable salts, solvates and prodrug forms, processes for the preparation thereof and their antiinflammatory effects and particularly to the inhibition of the production of the tumor necrosis factor-α (TNF-α) and of interleukin-1 (IL-1) and to their analgetic action.

Prior Art

Hitherto, 1-thiadibenzoazulenes, which are substituted in position 2 with methyl, methyl ketone, nitro group or a derivative of carboxylic group (Cagniant P. and Kirsch G., *C. R. Hebd. Sceances Acad.Sci.*, **1976,** *283*:638-686) have been described in the literature. According to our knowledge and available literature data, however, neither 1-thiadibenzoazulene derivatives of general formula I nor any possible methods of their preparation have been decribed so far. It is also not known either that 1-thiadibenzoazulenes possess an anti-inflammatory effect.

In 1975 TNF-α was defined as an endotoxine-induced serum factor causing tumor necrosis *in vitro* and *in vivo* (Carswell E. A. et al., *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*:36666-3670). In addition to antitumor activity, TNF-α has several other biologic activities, which are important in the homeostasis of organism as well as in pathophysiological conditions. The main sources of TNF-α are monocytes-macrophages, T-lymphocytes and mast cells.

The finding that anti-TNF-α antibodies (cA2) are effective in the treatment of patients suffering from rheumatoid arthritis (RA) (Elliott M. et al., *Lancet* **1994,** *344*:1105-1110) intensified the interest to find new TNF-α inhibitors as possible potent medicaments for RA. Rheumatoid arthritis is an autoimmune chronic inflammatory disease characterized by irreversible pathological changes of the joints. In addition to

RA, TNF-α antagonists are also applicable to several pathological conditions and diseases such as spondylitis, osteoarthritis, gout and other arthritic conditions, sepsis, septic shock, toxic shock syndrome, atopical dermatitis, contact dermatitis, psoriasis, glomerulonephritis, lupus erhythematosus, scleroderma, asthma, cachexia, chronic obstructive lung disease, congestive heart failure, insulin resistance, lung fibrosis, multiple sclerosis, Chron's disease, ulcerative colitis, viral infections and AIDS.

Proof of biological importance of TNF-α was obtained in *in vivo* experiments in mice having inactivated genes for TNF-α or its receptor. Such animals were resistant to collagen-induced arthritis (Mori L. et al., *J. Immunol.* **1996**, *157*:3178-3182) and to endotoxin-induced shock (Pfeffer K. et al., *Cell* **1993**, *73*:457-467). In experiments with animals having an increased TNF-α level a chronic inflammatory polyarthritis appeared (Georgopoulos S. et al., *J. Inflamm.* **1996**, *46*:86-97; Keffer J. et al., *EMBO J.* **1991**, *10*:4025-4031), which was palliated by inhibitors of TNF-α production. The treatment of such inflammatory and pathologic conditions usually includes the application of nonsteroid antiinflammatory medicaments, in severe cases, however, gold salts, D-penicillinamine or methotrexate are administered. Said medicaments act symptomatically and do not stop the pathological process. New approaches in theraphy of rheumatoid arthritis have been established upon medicaments such as tenidap, leflunomide, cyclosporine, FK-506 and biomolecules neutralizing the activity of TNF-α. Presently, the fusion protein of the soluble TNF receptor named etanercept (Enbrel, Immunex/Wyeth) and mouse and human cimeric monoclonal antibody named infliximab (Remicade, Centocor) are available on the market. In addition to RA-therapy, etanercept and infliximab are also approved for the treatment of Chron's disease (*Exp. Opin. Invest Drugs* **2000**, *9*, 103).

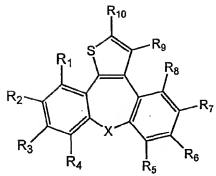
In RA-therapy, in addition to the inhibition of TNF-α secretion, it is also important to inhibit IL-1 secretion since IL-1 represents an important cytokine in cell regulation, immunoregulation and in the pathophysiological conditions such as inflammation (Dinarello C. A. et al., *Rev. Infect. Disease,* **1984**, *6*:51). Known biological activities of IL-1 are: activation of T-cells, induction of elevated temperature, stimulation of prostaglandine or collagenase secretion, chemotaxis of neutrophils and reduction of

iron level in plasma (Dinarello C. A., *J. Clinical Immunology,* **1985**, *5*:287). There are known two receptors to which IL-1 can be bound: IL-1RI and IL-1RII. IL-1RI transfers the signal intracellularly, while IL-1RII is present on the cell surface and does not transfer the signal within the cell. Since IL1-RII binds both IL-1 and IL1-RI, it can act as a negative regulator of IL-1 effect. In addition to the mentioned mechanism of regulation of signal transfer, another natural IL-1 receptor antagonist (IL-1ra) is present in cells. This protein binds to IL-1RI but does not transfer any signal. Yet its potency in the inhibition of signal transfer is not great, therefore it must be present in a 500 times higher concentration than IL-1 in order to break the signal transfer. Recombinant human IL-1ra (Amgen) was clinicaly tested (Bresnihan B. et al., *Arthrit. Rheum.* **1996**, *39*:73) and the obtained results demonstrated an improvement of the symptoms in 472 patients suffering from RA with respect to a placebo. These results indicate the importance of inhibition of IL-1 activity in the treatment of diseases such as RA where the production of IL-1 is inhibited. Due to the synergistic action of TNF-α and IL-1, dibenzoazulenes can be used in the treatment of conditions and diseases connected with an increased secretion of TNF-α and IL-1.

According to the known and established prior art, 1-thiadibenzoazulene compounds representing the subject of the present invention, their pharmacologically acceptable salts, hydrates, prodrug forms and pharmaceutical preparations comprising them have hitherto not been described. Moreover, no compound representing the subject of the present invention has been described either as an anti-inflammatory substance or as an inhibitor of TNF-α and IL-1 secretion or an analgetic.

Technical Solution

The present invention relates to compounds represented by the general formula **I**, 1-thiadibenzoazulene derivatives, to their pharmacologically acceptable salts and solvates represented by formula **I**



I

wherein

X can represent CH_2 or a heteroatom such as O, S, S(=O), S(=O)$_2$ or NR_{13}, wherein R_{13} means hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, arylcarbonyl, C_{1-6} alkylsulfonyl or arylsulfonyl and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 independently from each other represent substituents that can be hydrogen, halogens (fluorine, chlorine or bromine); or C_1-C_7 alkyls, alkenyls, aryls or heteroaryls; or can represent different groups: halomethyl, hydroxy, C_1-C_7 alkoxy or aryloxy, C_1-C_7 alkylthio or arylthio, C_1-C_7 alkylsulfonyl, ciano, amino, mono- and di-C_1-C_7 substituted amines, derivatives of carboxylic group (C_1-C_7 carboxylic acids and their anhydrides, C_1-C_7 unsubstituted, mono-, di-substituted amides, C_1-C_7 alkyl or aryl esters), C_1-C_7 derivatives of carbonyl group (C_1-C_7 alkyl or aryl carbonyls), and R_{10} can represent substituents such as: C_2-C_{15} alkyls, C_2-C_{15} alkenyls, C_2-C_{15} alkinyls, aryls or heteroaryls, C_1-C_{15} haloalkyls, C_1-C_{15} hydroxyalkyls, C_1-C_{15} alkyloxy, C_1-C_{15} alkylthio, C_3-C_{15} alkylcarbonyls, C_2-C_{15} alkylcarboxylic acid, C_2-C_{15} alkylsters, C_1-C_{15} alkylsulfonyls, C_1-C_{15} alkylarylsulfonyls, arysulfonyls and C_1-C_{15} alkylamines represented by the general formula

$$-(CH_2)_n\text{-}A$$

wherein

n means 1-15, and

one or more methylene groups can be substituted with an oxygen or sulfur atom, and

A represents a five- or six-membered, saturated or unsaturated ring with one, two or three heteroatoms, or

wherein R_{11} and R_{12} independently from each other represent hydrogen, C_1-C_7 alkyl, alkenyl, alkinyl, aryl or heteroaryl, or a heterocycle with 1-3 heteroatoms.

The terms as used in the present invention are defined as stated below unless otherwise specified.

"Alkyl" means a monovalent alkane (hydrocarbon), wherefrom a radical is derived, which can be a straight-chain, a branched-chain or a cyclic hydrocarbon or a combination of straight-chain and cyclic hydrocarbons and of branched-chain and cyclic hydrocarbons. The preferred straight-chain or branched-chain alkyls include methyl, ethyl, propyl, *iso*-propyl, butyl, *sec*-butyl and *t*-butyl. The preferred cycloalkyls include cyclopentyl and cyclohexyl. Alkyl also represents a straight-chain or branched-chain alkyl group containing a cycloalkyl portion or being broken by it.

"Alkenyl" means a hydrocarbon radical being a straight-chain, a branched-chain or a cyclic hydrocarbon or a combination of straight-chain and cyclic hydrocarbons and of branched-chain and cyclic hydrocarbons, which has at least one double carbon-carbon bond. Particularly ethenyl, propenyl, butenyl and cyclohexenyl are meant. As stated above under the definition of "alkyl", also alkenyl can be a straight-chain, a branched-chain or a cyclic one, and a portion of alkenyl group can contain double bonds and it can also be substituted when a substituted alkenyl group is of interest. Alkenyl also represents a straight-chain or a branched-chain alkenyl group containing a cycloalkenyl portion or being broken by it.

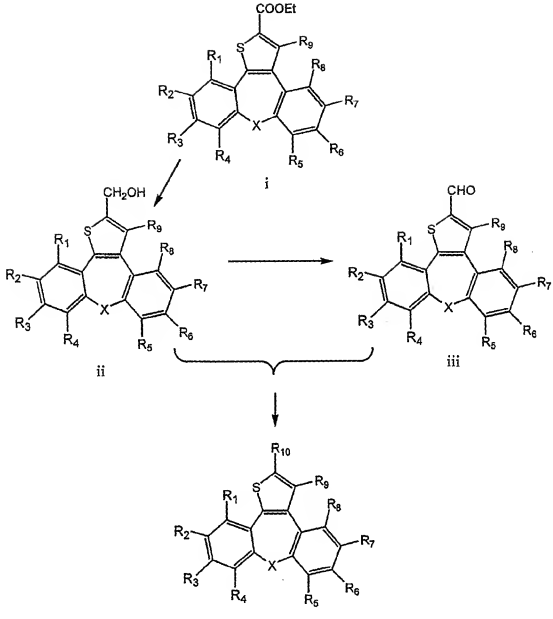
"Alkinyl" means a hydrocarbon radical, which is a straight-chain or a branched-chain one and contains at least one and at most three triple carbon-carbon bonds. Particularly ethinyl, propinyl and butinyl groups are meant.

"Aryl" means an aromatic ring such as phenyl, substituted phenyl or similar groups as well as fused rings such as naphtyl etc. Aryl contains at least one ring with at least 6

carbon atoms or two rings having together 10 carbon atoms and alternating double (resonant) bonds between carbon atoms (particularly phenyl and naphtyl). Aryl groups can be additionally substituted with one or two substituents such as halogens (fluorine, chlorine and bromine), hydroxy, C_1-C_7 alkyls, C_1-C_7 alkoxy or aryloxy, C_1-C_7 alkylthio or arylthio, alkylsulfonyl, ciano or amino groups.

"Heteroaryl" means a monocyclic or a bicyclic aromatic hydrocarbon containing at least one heteroaom such as O, S or N with carbon and nitrogen representing the binding sites for the basic formula. Heteroaryl can be additionally substituted with a halogen or CF_3 group and a lower alkyl such as methyl, ethyl or propyl. Heteroaryl means an aromatic and a partly aromatic group with one or more heteroatoms. Examples of this type are thiophene, pyrrole, imidazole, pyridine, oxazole, thiazole, pyrazole, tetrazole, pyrimidine, pyrazine and triazine.

Another object of the present invention relates to a process for the preparation of dibenzoazulene derivatives represented by formula **I**. These compounds can be prepared from thiophene esters of the general formula **I**, wherein all radicals and symbols have the above-defined meanings i.e. where radicals R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 have the above-defined meanings and R_{10} means ethoxycarbonyl (Cagniant P. and Kirsch G., *C. R. Hebd. Sceances Acad. Sci.*, **1976**, *283*:683-686). By means of further reactions these esters are converted into other substituents defined as R_{10}. These reactions include the reduction of an ester to the corresponding alcohol or aldehyde, alkylation and other nucleophilic reactions on the ethoxycarbonyl group (Scheme 1).



Scheme 1

The reduction of the ethoxycarbonyl group is performed by the use of metal hydrides to obtain an alcohol (R_{10} = hydroxymethyl). The reaction is performed in suitable nonpolar solvents (preferably in aliphatic ethers) at a temperature from 0 to 36°C within a period of 1 to 5 hours. The isolation and purification of the compounds can be performed by recrystallization or column chromatography.

By the reaction of an alcohol of the general formula **I** wherein R_{10} represents hydroxymethyl and of a chloride of the formula **II**

$$Cl\text{-}(CH_2)_n\text{-}A \qquad \textbf{II}$$

wherein the symbols n and A have the above-defined meanings,

ω-amino ethers of the general formula **I** are obtained.

The stated reactions are performed at a temperature from 20 to 100 °C within a period of 1 to 24 hours under the conditions of phase-transfer catalysis in a two-phase system (preferably 50% NaOH-toluene) and in the presence of a phase-transfer catalyst (preferably benzyl-triethyl-ammonium-chloride, benzyl-triethyl-ammonium-bromide, cetyl-trimethyl-bromide). Subsequently to the treatment of the reaction mixture, the obtained products are isolated by recrystallization or chromatography on a silica gel column.

By the oxidation of an alcohol of the general formula **I** wherein R_{10} = hydroxymethyl with pyridinyl dichromate or pyridinyl chlorochromate, an aldehyde the general formula **I** wherein R_{10} = CHO is obtained. The reaction is performed in dichloromethane at room temperature within a period of 2 to 5 hours. The obtained aldehyde is purified by passing through a column of florisil or silica gel.

The reaction of an aldehyde of the general formula **I** wherein R_{10} = CHO with different corresponding phosphorus-ylides results in the formation of compounds of the general formula **I**, wherein R_{10} has the above-defined meanings and which have an alkene functionality in the position 2 of the chain defining R_{10}. These reactions are performed in anhydrous solvents such as toluene, benzene or hexane at the reflux temperature of the solvent within a period of 3 to 5 hours. The obtained products are purified by column chromatography.

By the hydrogenation of the compounds **I**, wherein R_{10} contains one or more double carbon-carbon bonds, compounds of the general formula **I** wherein R_{10} has a saturated chain are obtained. These reactions are usually performed with 5% Pd on active

charcoal under a hydrogen pressure from $6.7x10^4$ to $4.0x10^5$ Pa in ethanol, ethyl acetate or other suitable solvents. By filtration and evaporation of the solvents saturated products are obtained, which can be purified to the desired purity by recrystallization or column chromatography on silica gel.

The pharmaceutically suitable salts of the compounds representing a subject of the present invention include salts with inorganic acids (hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids) or organic acids (tartaric, acetic, trifluoroacetic, citric, maleic, lactic, fumaric, benzoic, succinic, methanesulfonic and p-toluenesulfonic acids).

A further subject of the present invention is the use of the compounds of the present invention in the treatment of inflammatory diseases and conditions, particularly of all diseases and conditions induced by an excessive secretion of TNF-α and IL-1.

An effective dose of the cytokine or inflammation mediator production inhibitors of the present invention or of pharmaceutically acceptable salts thereof is useful in the production of medicaments for the treatment and prophylaxis of any pathological condition or disease induced by an excessive unregulated production of cytokines or inflammation mediators.

More specifically, the present invention relates to an effective dose of TNF-α inhibitors, which can be determined by common methods.

Further, the present invention relates to pharmaceutical preparations containing an effective nontoxic dose of compounds of the present invention as well as pharmaceutically acceptable carriers and solvents.

The preparation of the pharmaceutical preparations can include mixing, granulating, tabletting and dissolving the ingredients. Chemical carriers can be in solid or liquid form. Solid carriers can be lactose, sucrose, talc, gelatine, agar, pectin, magnesium

stearate, fatty acids etc. Liquid carriers can be syrups, oils such as olive, sunflower seed or soybean oils, water etc. Similarly, carriers may also contain a component for a sustained release of the active component such as glyceryl monostearate or glyceryl distearate. Several forms of pharmaceutical compositions can be prepared. If a solid carrier is used these forms can include tablets, solid gelatinous capsules, powders or granules that can be administered orally in capsules. The amount of the solid carrier can vary but mainly it is in the range from 25 mg to 1 g. If a liquid carrier is used, the preparation can be in the form of a syrup, emulsion, soft gelatinous capsules, sterile injectable liquids such as ampules, or nonaqueous liquid suspensions.

The compounds of the present invention can be administered orally, parenterally, topically, intranasally, intrarectally and intravaginally. "Parenterally" means intraveneous, intramuscular and subcutaneous administrations. The corresponding preparations of the compounds of the present invention can be used in the prophylaxis as well as in the treatment of several diseases and pathological inflammatory conditions caused by an excessive nonregulated production of cytokines or inflammation mediators, foremost TNF-α. They include rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic pathological conditions and diseases, eczema, psoriasis as well as other inflammatory conditions of skin such as burns induced by UV radiation (sun rays and similar UV sources), inflammatory eye diseases, Chron's disease, ulcerative cholitis and asthma.

The inhibitory effect of the compounds of the present invention on the secretion of TNF-α and IL-1 was determined by the following *in vitro* and *in vivo* experiments:

Determination of TNF-α and IL-1 secretion in mononuclear cells of human peripheral blood *in vitro*

Peripheral blood mononuclear cells (PMBC) were prepared from heparinized whole blood after separation of PMBC on Ficoll-Hypaque (Amersham-Pharmacia). For the determination of TNF-α level $3.5\text{-}5x10^4$ cells were cultured in a total volume of 200 μl within a period of 18 to 24 hours on microtiter flat bottom plates (96 wells, Falcon) in RPMI 1640 medium supplemented with 10% of heat-inactivated human AB serum (Hrvatski zavod za transfuzijsku medicinu, Zagreb), 100 units/ml of penicillin, 100 mg/ml of streptomycine and 20 mM HEPES (GIBCO). The cells were incubated at 37°C in an atmosphere with 5% CO_2 and 90% moisture. The cells in a negative control were cultured only in the medium (NC), while the secretion of TNF-α in a positive control was stimulated by the addition of 1 μg/ml lipopolysaccharide (LPS, E. coli serotype 0111:B4, SIGMA) (PC) and the effect of the tested substances on TNF-α secretion was tested after their addition to cell cultures stimulated with LPS (TS). The TNF-α level in the cell supernatant was determined by ELISA according to the manufacturer's (R&D Systems) suggestions. The test sensitivity was <3pg/ml TNF-α. The determination of IL-1 level was performed as described for TNF-α determination, only that $1x10^5$ cells/well and 0.1ng/ml of LPS were used. IL-1 level was determined by ELISA (R&D Systems). The percentage inhibition of TNF-α or IL-1 production was calculated by the following equation:

$$\% \text{ inhibition} = [1-(TS-NC)/(PC-NC)]*100.$$

IC-50 value was defined as the concentration of the substance at which 50% of TNF-α production was inhibited. The compounds demonstrating IC-50 in concentrations of 20 μM or lower were considered active.

Determination of TNF-α and IL-1 secretion by mouse peritoneal macrophages *in vitro*

For obtaining peritoneal macrophages, male BALB/c mice at an age of 8 to 12 weeks were injected i.p. with 300 μg of zimozane (SIGMA) dissolved in a phosphate buffer (PBS) in a total volume of 0.1 ml/mouse. After 24 hours the mice were subjected to euthanasia according to the Laboratory Animals Welfare Act. The peritoneal cavity was washed with 5 ml of sterile saline. The obtained peritoneal macrophages were washed twice with sterile saline and after the last centrifugation (800 g) they were resuspended in RPMI 1640. For the determination of TNF-α secretion, $5x10^4$ cells/well were cultured in a total volume of 200 μl within a period of 18 to 24 hours on microtiter flat bottom plates (96 wells, Falcon) in RPMI 1640 medium supplemented with 10% of heat-inactivated fetal calf serum (FCS), 100 units/ml of penicillin, 100 mg/ml of streptomycine, 20 mM HEPES and 50 μM 2-β mercaptoethanol (all of GIBCO). The cells were incubated at 37°C in an atmosphere with 5% CO_2 and 90% moisture. The cells in a negative control were cultured only in the medium (NC), while the secretion of TNF-α in a positive control was stimulated by the addition of 1 μg/ml lipopolysaccharide (LPS, E. coli serotype 0111:B4, SIGMA) (PC) and the effect of the tested substances on TNF-α secretion was tested after their addition to cell cultures stimulated with LPS (TS). The TNF-α level in the cell supernatant was determined by ELISA according to manufacturer's (R&D Systems, Biosource) suggestions. The determination of IL-1 level was performed as described for TNF-α determination, only that $1x10^5$ cells/well and 0.1 ng/ml of LPS were used. The IL-1 level was determined by ELISA (R&D Systems). The percentage inhibition of TNF-α or IL-1 production was calculated by the following equation:

$$\% \text{ inhibition} = [1-(TS-NC)/(PC-NC)]*100.$$

IC-50 value was defined as the concentration of the substance at which 50% of TNF-α production was inhibited. The compounds demonstrating IC-50 in concentration of 10 μM or lower were considered active.

***In vivo* model of LPS-induced exccessive secretion of TNF-α or IL-1 in mice**

TNF-α or IL-1 secretion in mice was induced according to the previously described method (Badger A. M. et al., *J. of Pharmac. and Env. Therap.* **1996**, *279*:1453-1461). In the test male BALB/c mice at an age of 8 to 12 weeks in groups of 6 to 10 animals were used. Animals were treated p.o. either only with the solvent (in a negative and a positive control) or with solutions of the substance 30 minutes prior to the i.p. treatment with LPS (E.coli serotype 0111:B4, Sigma) in a dose of 25 μg/animal. Two hours later the animals were euthanized by means of an i.p. injection of Roumpun (Bayer) and Ketanest (Park-Davis). A blood sample from each animal was collected in a "vacutaner" tube (Becton Dickinson) and the plasma was separated according to the manufacturer's suggestions. The TNF-α level in the plasma was determined by ELISA (Biosource, R&D Systems) according to the process prescribed by the manufacturer. The test sensitivity was <3pg/ml TNF-α. The IL-1 level was determined by ELISA (R&D Systems). The percentage inhibition of TNF-α or IL-1 production was calculated by the following equation:

$$\% \text{ inhibition} = [1-(TS-NC)/(PC-NC)]*100.$$

The compounds demonstrating a 30% or higher inhibition of TNF-α production at a dose of 10 mg/kg were considered active.

Writhing test for analgetic activity

In this test, pain is induced with an injection of an irritant, usually acetic acid, into the peritoneal cavity of mice. The animals respond by the characteristic writhings, which gave the name of the test. (Collier H. O. J. et al., *Pharmac. Chemother.*, **1968**, *32*:295-310; Fukawa K. et al., *J. Pharmacol. Meth.*, **1980**, *4*:251-259; Schweizer A. et al, *Agents Actions*, **1988**, *23*:29-31). This test is suitable for the determination of analgetic activity of compounds. Process: male BALB/c mice (Charles River, Italy) at an age of 8 to 12 weeks were used. To a control group methyl cellulose was administered p.o. 30 minutes prior to i.p. administration of acetic acid in a concentration of 0.6%, whereas to the test groups a standard (acetyl salicylic acid) or test substances in

methylcellulose were administered p.o. 30 minutes prior to i.p. administration of 0.6% acetic acid (volume 0.1 ml/10 g). Mice were individually placed under glass funnels und the number of writhings of each animal was recorded during a period of 20 minutes. The percentage inhibition of writhings was calculated according to the equation:

% inhibition = (mean value of number of writhings in the control group – number of writhings in the test group)/number of writhings in the control group*100.

The compounds demonstrating the same or better analgetic activity than acetyl salicylic acid were considered active.

***In vivo* model of LPS-induced shock in mice**

Male BALB/c mice at an age of 8 to 12 weeks (Charles River, Italy) were used. LPS isolated from *Serratie marcessans* (Sigma, L-6136) was diluted in sterile saline. The first LPS injection was administered intradermally in a dose of 4μg/mouse. 18 to 24 hours later LPS was administered i.v. in a dose of 200 μg/mouse. To a control group two LPS injections were administered in the above described manner. The test groups were administered the substances p.o. half an hour prior to each LPS administration. The survival after 24 hours was observed.
The compounds resulting in a 40% or better survival at a dose of 30 mg/kg were considered active.

The compounds of Examples 1, 5, 19 and 21 demonstrate activity in at least two investigated tests. These results, however, only illustrate the biological activity of the compounds and do not limit the present invention in any way.

Preparation processes with Examples

The present invention is illustrated but in no way limited by the following Examples.

Example A
Preparation of alcohol

To a suspension of $LiAlH_4$ in dry ether (10 mmole/15 ml of dry ether) an ether solution of an ester (2 mmole/15 ml dry ether) was added dropwise. The reaction mixture was stirred at room temperature for 4 hours. Subsequently, when all ester was consumed in the reaction (the course of the reaction was followed by thin layer chromatography), the excess of $LiAlH_4$ was decomposed by the addition of diethyl ether and water. The obtained white precipitate was filtered off and, after drying over anhydrous Na_2SO_4, the filtrate was evaporated under the reduced pressure. The crude product was purified by column chromatography.

According to the process of Example A and starting from corresponding esters, dibenzoazulene alcohols represented by the formula **I**, wherein R_1, R_5, R_6, R_7, R_8 and R_9 = H, and R_2, R_3, R_4 and X have the meanings as illustrated in Table 1, were prepared.

Table 1

Comp.	X	R_2	R_3	R_4	m.p.(°C)	^{1}H NMR (ppm, $CDCl_3$)
1	O	H	H	H	120-122	2.13 (s, 1H); 4.85 (s, 2H); 7.12-7.43(m, 9H)
2	O	H	H	Cl	131-133	1.88 (s, 1H); 4.94 (s, 2H); 7.1-7.6 (m,8H)
3	O	Cl	H	H	157-158	1.72 (s, 1H); 4.91 (s, 2H); 7.2-7.5 (m,8H)
4	O	F	H	H	117-123	1.74 (s, 1H); 4.91 (s,2H); 7.0-7.46 (m, 8H)
5	S	H	H	H	-	2.14 (s, 1H);4.88 (s, 2H); 7.2-7.6 (m,9H)
6	S	F	H	H	124-128	1.79 (s, 1H); 4.93 (s, 2H); 6.9-7.6 (m,8H)
7	S	Cl	H	H	122	1.96 (s, 1H); 4.92 (s, 2H); 7.2-7.6 (m,8H)
8	S	Br	H	H	-	1.77 (s, 1H); 5.01 (s, 2H); 7.3-7.7 (m, 8H)
9	S	H	CF_3	H	-	3.3 (s, 1H); 4.95 (s, 2H); 7.32-7.57 (m, 4H); 7.59 (s, 1H); 7.62-7.66 (m, 2H); 7.9 (s, 1H)
10	S	H	Cl	H	-	1.75 (s, 1H); 4.92 (s, 2H); 7.23-7.66 (m, 8H)
11	S	H	Br	H	-	1.67 (s, 1H); 4.93 (s, 2H); 7.23-7.81 (m, 8H)
12	S	CH_3	H	CH_3	-	1.8 (s, 1H); 2.29 (s, 3H); 2.61 (s, 3H); 4.91 (s, 7.1 (s, 1H); 7.18 (s, 1H); 7.22 (s, 1H); 7.27-7.71 (m, 4H)
13	S	Cl	Cl	H	-	1.72 (s, 1H); 4.94 (s, 2H); 7.24 (s, 1H); 7.29-7.54 (m, 3H); 7.58 (s, 1H); 7.60-7.65 (m, 1H); 7.74 (s, 1H)
14	S	F	H	Cl	-	2.07 (s, 1H); 4.96 (s, 2H); 6.96-7.96 (m, 7H)

The compounds decribed in Examples 1-5 were prepared from alcohol **1** and the corresponding chloroalkyldialkyamine hydrochloride according to the process described in Example 1.

Example 1

Dimethyl-[3-(8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-amine hydrochloride

To a solution of 3-dimethylaminopropylchloride hydrochloride (2.2 g, 0.014 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.1 g, 0.44 mmole) and a toluene solution of alcohol **1** (0.28 g, 0.001 mole) were added. The reaction mixture was heated under vigorous stirring and reflux for 4 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product (0.25 g) was isolated. By the addition of concentrated hydrochloric acid into the cold ethanol solution of amine, a crystalline product, m.p. 162-165°C, was obtained.

C, H, N, S analysis: C 65.45 (calc. 65.74); H 6.12 (calc. 6.02); N 3.89 (calc. 3.48); S 8.52 (calc. 7.98)
^{1}H NMR (ppm, $CDCl_3$): 2.18 (m, 2H); 2.79 (d, 6H); 3.15 (m, 2H); 3.68 (t, 2H); 4.71 (s, 2H); 7.15-7.58 (m, 9H), 12.29 (s, 1H).

Example 2

Dimethyl-[2-(8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-amine hydrochloride

By the reaction of alcohol **1** (0.45 g, 0.0015 mole) and 2-dimethylaminoethylchloride hydrochloride (3.05 g, 0.021 mole), an oily product (0.3 g) was obtained, which was converted into the hydrochloride, m.p. 203°C.

C, H, N analysis: C 64.85 (calc. 65.02); H 5.80 (calc. 5.72); N 3.48 (calc. 3.61).
^{1}H NMR (ppm, $CDCl_3$): 2.89 (s, 6H); 3.27 (m, 2H); 4.07 (m, 2H); 4.78 (s, 2H); 7.16-7.47 (m, 9H); 12.5 (s, 1H).

Example 3

4-[2-(8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine hydrochloride

By the reaction of alcohol **1** (0.45 g, 0.0015 mole) and 4-(2-chloroethyl)-morpholine hydrochloride (3.9 g, 0.021 mole), an oily product (0.34 g) was obtained, which was converted into the hydrochloride, m.p. 164°C.

C, H, N analysis: C 63.57 (calc. 64.25); H 5.76 (calc. 5.6); N 3.79 (calc. 3.26).
^{1}H NMR (ppm, $CDCl_3$): 2.99 (bs, 2H); 3.23 (m, 2H); 3.55 (d, 2H); 3.94 (d, 2H); 4.14 (m, 2H); 4.27 (m, 2H); 4.75 (s, 2H); 7.14-7.44 (m, 9H); 13.16 (s, 1H).

Example 4

1-[2-(8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride

By the reaction of alcohol **1** (0.45 g, 0.0015 mole) and 1-(2-chloroethyl)-piperidine monohydrochloride (3.86 g, 0.021mole), an oily product (0.48 g) was obtained, which was converted into the hydrochloride, m.p. 179°C.

C, H, N analysis: C 67.53 (calc. 67.35); H 6.30 (calc. 6.12); N 3.61 (calc. 3.27).
^{1}H NMR (ppm, $CDCl_3$): 1.83 (m, 4H); 2.25 (m, 2H); 2.74 (m, 2H); 3.18 (m, 2H); 3.6 (m, 2H); 4.10 (m, 2H); 4.73 (s, 2H); 7.13-7.5 (m, 9H); 12.15 (s, 1H).

Example 5

1-[2-(8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride

By the reaction of alcohol **1** (0.45 g, 0.0015 mole) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (3.6 g, 0.021 mole), an oily product (0.41 g) was obtained, which was converted into the hydrochloride, m.p. 203-205°C.

C, H, N analysis: C 67.12 (calc. 67.35); H 6.03 (calc. 5.84); N 3.91 (calc. 3.38).
^{1}H NMR (ppm, $CDCl_3$): 2.02 (m, 2H); 2.18 (m, 2H); 2.91 (m, 2H); 3.27 (m, 2H); 3.81 (m, 2H); 4.08 (m, 2H); 4.75 (s, 2H); 7.12-7.5 (m, 9H); 12.7 (s, 1H).

The compounds described in Examples 6-10 were prepared from alcohol **2** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 6.

Example 6

[3-(9-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine

To a solution of 3-dimethylaminopropylchloride hydrochloride (2.37 g, 0.015 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.25 g) and a toluene solution of alcohol **2** (0.2 g, 0.64 mmole) were added. The reaction mixture was heated under vigorous stirring and reflux for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product (0.11 g) was isolated.

^{1}H NMR (ppm, $CDCl_3$): 1.93 (m, 2H); 2.39 (s, 6H); 2.59 (m, 2H); 3.64 (m, 2H); 4.72 (s, 2H); 7.05-7.56 (m, 8H).

Example 7

[2-(9-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine

By the reaction of alcohol **2** (0.2 g, 0.64 mmole) and 2-dimethylaminoethylchloride hydrochloride (2.6 g, 0.015 mole), an oily product (0.15 g) was obtained.

^{1}H NMR (ppm, $CDCl_3$): 2.42 (s, 6H); 2.72 (m, 2H); 3.74 (m, 2H); 4.76 (s, 2H); 7.08-7.55 (m, 8H).

Example 8

4-[2-(9-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine

By the reaction of alcohol **2** (0.2 g, 0.64 mmole) and 4-(2-chloroethyl)-morpholine hydrochloride (2.8 g, 0.015 mole), an oily product (0.19 g) was obtained.

^{1}H NMR (ppm, $CDCl_3$): 2.51 (m, 4H); 3.71 (m, 8H); 4.75 (s, 2H); 7.08-7.56 (m, 8H).

Example 9

1-[2-(9-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine

By the reaction of alcohol **2** (0.2 g, 0.64 mmole) and 1-(2-chloroethyl)-piperidine monohydrochloride (2.76 g, 0.015 mole), an oily product (0.13 g) was obtained.

Example 10

1-[2-(9-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine

By the reaction of alcohol **2** (0.2 g, 0.64 mmole) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (2.55 g, 0.015 mole), an oily product (0.15 g) was obtained.

^{1}H NMR (ppm, $CDCl_3$): 2.02 (m, 2H); 2.2 (m, 2H); 2.94 (m, 2H); 3.32 (m, 2H); 3.87 (m, 2H); 4.11 (m, 2H); 4.79 (s, 2H); 7.07-7.56 (m, 8H).

The compounds described in Examples 11-15 were prepared from alcohol **3** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 11.

Example 11

[3-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine

To a solution of 3-dimethylaminopropylchloride hydrochloride (2.2 g, 0.014 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.25 g) and a toluene solution of alcohol **3** (0.19 g, 0.6 mmole) were added. The reaction mixture was heated under vigorous stirring and reflux for 5 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product (0.18 g) was isolated.

^{1}H NMR (ppm, $CDCl_3$): 2.05-2.14 (m, 2H); 2.63 (s, 6H); 2.91 (t, 2H); 3.71 (t, 2H); 4.74 (s, 2H); 7.2-7.5 (m, 8H).

Example 12

[2-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine

By the reaction of alcohol **3** (0.19 g, 0.6 mmole) and 2-dimethylaminoethylchloride hydrochloride (2.01 g, 0.014 mole), an oily product (0.2 g) was obtained.

^{1}H NMR (ppm, $CDCl_3$): 2.46 (s, 6H); 2.80 (t, 2H); 3.78 (t, 2H); 4.76 (s, 2H); 7.19-7.5 (m, 8H).

Example 13

4-[2-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine

By the reaction of alcohol **3** (0.19 g, 0.6 mmole) and 4-(2-chloroethyl)-morpholine hydrochloride (2.8 g, 0.015 mole), an oily product (0.3 g) was obtained.

^{1}H NMR (ppm, $CDCl_3$): 2.61-2.84 (m, 6H); 3.82 (m, 6H); 4.77 (s, 2H); 7.2-7.48 (m, 8H).

Example 14

1-[2-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine

By the reaction of alcohol **3** (0.19 g, 0.6 mmole) and 1-(2-chloroethyl)-piperidine monohydrochloride (2.76 g, 0.015 mole), an oily product (0.21 g) was obtained.

^{1}H NMR (ppm, $CDCl_3$): 1.43 (m, 2H); 1.85 (m, 2H); 2.25 (m, 2H); 2.75 (m, 2H); 3.14 (m, 2H); 3.65 (m, 2H); 4.01-4.15 (m, 2H); 4.84 (s, 2H); 7.15-7.65 (m, 8H).

Example 15

1-[2-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine

By the reaction of alcohol **3** (0.19 g, 0.6 mmole) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (2.55 g, 0.015 mole), an oily product (0.25 g) was obtained.

^{1}H NMR (ppm, $CDCl_3$): 1.8-2.2 (m, 8H); 2.9-3.25 (m, 2H); 3.98 (m, 2H); 4.8 (s, 2H); 7.19-7.45 (m, 8H).

The compounds described in Examples 16-20 were prepared from alcohol **4** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 16.

Example 16

[3-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethylamine hydrochloride

To a solution of 3-dimethylaminopropylchloride hydrochloride (2.2 g, 0.014 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.15 g) and a toluene solution of alcohol **4** (0.2 g, 0.63 mmole) were added. The reaction mixture was heated under vigorous stirring and reflux for 4 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product (0.14 g) was isolated.

Example 17

[2-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride

By the reaction of alcohol **4** (0.2 g, 0.63 mmole) and 2-dimethylaminoethylchloride hydrochloride (2.01 g, 0.014 mole), an oily product (0.24 g) was obtained, which was converted into the hydrochloride, m.p. 178-179°C.

C, H, N, S analysis: C 61.53 (calc. 62.14); H 5.19 (calc. 5.21); N 3.72 (calc. 3.45); S 8.15 (calc. 7.90).

^{1}H NMR (ppm, $CDCl_3$): 2.91 (d, 6H); 3.28 (m, 2H); 4.10 (m, 2H); 4.79 (s, 2H); 6.97-7.5 (m, 8H); 12.75 (s, 1H).

Example 18

4-[2-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine hydrochloride

By the reaction of alcohol **4** (0.2 g, 0.63 mmole) and 4-(2-chloroethyl)-morpholine hydrochloride (2.6 g, 0.014 mole), an oily product (0.25 g) was obtained, which was converted into the hydrochloride, m.p. 207-208°C.

C, H, N, S analysis: C 61,28 (calc. 61.67); H 5.33 (calc. 5.18); N 3.36 (calc. 3.13); S 7.44 (calc. 7.16).
^{1}H NMR (ppm, $CDCl_3$): 3.05 (m, 2H); 3.25 (m, 2H); 3.57 (d, 2H); 3.97 (d, 2H); 4.19 (m, 2H); 4.35 (m, 2H); 4.79 (s, 2H); 7.0-7.47 (m, 8H).

Example 19

1-[2-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride

By the reaction of alcohol **4** (0.2 g, 0.63 mmole) and 1-(2-chloroethyl)-piperidine monohydrochloride (2.6 g, 0.014 mole), an oily product (0.2 g) was obtained, which was converted into the hydrochloride, m.p. 122-124°C.

^{1}H NMR (ppm, $CDCl_3$): 1.95 (m, 4H); 2.17 (m, 2H); 2.27 (m, 2H); 2.75 (m, 2H); 3.12 (m, 2H); 3.65 (d, 2H); 4.78 (s, 2H); 6.98-7,68 (m, 8H); 12.2 (s, 1H).

Example 20

1-[2-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride

By the reaction of alcohol **4** (0.2 g, 0.63 mmole) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (2.4 g, 0.014 mole), an oily product (0.27 g) was obtained, which was converted into the hydrochloride, m.p. 210°C.

C, H, N, S analysis: C 63.02 (calc. 63.95); H 5.42 (calc. 5.37); N 3.48 (calc 3.24); S 7.62 (calc. 7.42).
^{1}H NMR (ppm, $CDCl_3$): 2.09 (m, 2H); 2.17 (m, 2H); 2.94 (m, 2H); 3.31 (m, 2H); 3.85 (m, 2H); 4.10 (m, 2H); 4.79 (s, 2H); 6.97-7.48 (m, 8H); 12.3 (s, 1H).

The compounds described in Examples 21-25 were prepared from alcohol **5** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 21.

Example 21

[3-(1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethylamine hydrochloride

To a solution of 3-dimethylaminopropylchloride hydrochloride (2.2 g, 0.012 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.15 g, 0.65 mmole) and a toluene solution of alcohol **5** (0.33 g, 0.0011 mole) were added. The reaction mixture was heated under vigorous stirring and reflux for 5 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product (0.32 g) was isolated. By the addition of concentrated hydrochloric acid into the cold ethanol solution of amine, a crystalline product was obtained.

C, H, N, S analysis: C 62.74 (calc. 63.21); H 5.83 (calc. 5.79); N 3.63 (calc. 3.35); S 15.51 (calc. 15.34).
^{1}H NMR (ppm, $CDCl_3$): 2.20 (m, 2H); 2,80 (d, 6H); 3.17 (m, 2H); 3.72 (m, 2H); 4.73 (s, 2H); 7.11-7.63 (m, 9H); 12.27 (s, 1H).

Example 22

[2-(1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethylamine hydrochloride

By the reaction of alcohol **5** (0.25 g, 0.84 mmole) and 2-dimethylaminoethylchloride hydrochloride (2.7 g, 0.019 mole), an oily product (0.22 g) was obtained, which was converted into the hydrochloride, m.p. 151°C .

^{1}H NMR (ppm, $CDCl_3$): 2.90 (m, 6H); 3.28 (m, 2H); 4.12 (m, 2H); 4.80 (s, 2H); 7.23-7.66 (m, 9H); 12.7 (s, 1H).

Example 23

4-[2-(1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine hydrochloride

By the reaction of alcohol **5** (0.25 g, 0.84 mmole) and 4-(2-chloroethyl)-morpholine hydrochloride (3.47 g, 0.019 mole), an oily product (0.3 g) was obtained, which was converted into the hydrochloride, m.p. 178-183°C.

C, H, N, S analysis: C 59,76 (calc. 61.93); H 5.30 (calc. 5.42); N 3.35 (calc. 3.14); S 13.89 (calc. 14.38).
^{1}H NMR (ppm $CDCl_3$): 3.05 (m, 2H); 3.25 (m, 2H); 3.55 (m, 2H); 4.0 (m, 2H); 4.15-4.38 (m, 4H); 4.7 (s, 2H); 7.22-7.65 (m, 9H); 13.25 (s, 1H).

Example 24

1-[2-(1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride

By the reaction of alcohol **5** (0.25 g, 0.84 mmole) and 1-(2-chloroethyl)-piperidine monohydrochloride (3.3 g, 0.018 mole), an oily product (0.17 g) was obtained, which was converted into the hydrochloride, m.p. 173°C.

^{1}H NMR (ppm, $CDCl_3$): 1.46 (m, 2H); 1.95 (m, 4H); 2.27 (m, 2H); 2.85 (m, 2H); 3.32 (m, 2H); 3.68 (m, 2H); 4.12 (m, 2H); 7.22-7.35 (m, 9H); 10.97 (s, 1H).

Example 25

1-[2-(1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride

By the reaction of alcohol **5** (0.25 g, 0.84 mmole) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (3.1 g, 0.019 mole), an oily product (0.2 g) was obtained, which was converted into the hydrochloride.

The compounds described in Examples 26-30 were prepared from alcohol **6** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 26.

Example 26

[3-(11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride

To a solution of 3-dimethylaminopropylchloride hydrochloride (1.8 g, 0.011 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.15 g) and a toluene solution of alcohol **6** (0.25 g, 0.8 mmole) were added. The reaction mixture was heated under vigorous stirring and reflux for 5 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product (0.18 g) was isolated. By the addition of concentrated hydrochloric acid into the cold ethanol solution of amine, a crystalline product was obtained, m.p. 209-214°C.

^{1}H NMR (ppm, $CDCl_3$): 2.30 (m, 2H); 2.88 (d, 6H); 3.24 (m, 2H); 3.80 (m, 2H); 4.82 (s, 2H); 7.08 (m, 1H); 7.28-7.71 (m, 7H); 12.5 (s, 1H).

Example 27

[2-(11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride

By the reaction of alcohol **6** (0.21 g, 0.67 mmole) and 2-dimethylaminoethylchloride hydrochloride (1.5 g, 0.01 mole), an oily product (0.22 g) was obtained, which was converted into the hydrochloride, m.p. 151-155°C.

^{1}H NMR (ppm, $CDCl_3$): 2.23 (s, 6H); 3.03 (m, 2H); 4.22 (m, 2H); 4.87 (s, 2H); 7.06-7.12 (m, 1H); 7.23-7.73 (m, 7H); 12.5 (s, 1H).

Example 28

4-[2-(11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine hydrochloride

By the reaction of alcohol **6** (0.21 g, 0.67 mmole) and 4-(2-chloroethyl)-morpholine hydrochloride (1.9 g, 0.01 mole), an oily product (0.15 g) was obtained, which was converted into the hydrochloride, m.p. 168-170°C.

^{1}H NMR (ppm, $CDCl_3$): 3.05 (m, 4H); 3.65 (m, 2H); 4.05 (m, 2H); 4.28 (m, 4H); 4.87 (s, 2H); 7.09 (m, 1H); 7.23-7.74 (m, 7H); 13.25 (s, 1H).

Example 29

1-[2-(11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride

By the reaction of alcohol **6** (0.21 g, 0.67 mmole) and 1-(2-chloroethyl)-piperidine monohydrochloride (1.9 g, 0.01 mole), an oily product (0.2 g) was obtained, which was converted into the hydrochloride, m.p. 214-216°C.

Example 30

1-[2-(11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride

By the reaction of alcohol **6** (0.21 g, 0.67 mmole) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (1.8 g, 0.01 mole), an oily product (0.17 g) was obtained, which was converted into the hydrochloride, m.p. 202-205°C.

^{1}H NMR (ppm, $CDCl_3$): 2.14 (m, 2H); 2.24 (m, 2H); 3.01 (m, 2H); 3.85 (m, 2H); 3.93 (m, 2H); 4.21 (m, 2H); 4.88 (s, 2H); 7.09 (m, 1H); 7.24-7.69 (m, 7H); 12.7 (s, 1H).

The compounds described in Examples 31-35 were prepared from alcohol **7** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 31.

Example 31

[3-(11-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride

To a solution of 3-dimethylaminopropylchloride hydrochloride (1.7 g, 0.011 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.15 g) and a toluene solution of alcohol **7** (0.25 g, 0.75 mmole) were added. The reaction mixture was heated under vigorous stirring and reflux for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product (0.17 g) was isolated, which was converted into the hydrochloride, m.p. 199-200°C.

^{1}H NMR (ppm, $CDCl_3$): 2.31 (m, 2H); 2.89 (d, 6H); 3.25 (m, 2H); 3.80 (m, 2H); 4.8 (s, 2H); 7.26-7.69 (m, 8H); 12.5 (s, 1H).

Example 32

[2-(11-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride

By the reaction of alcohol **7** (0.25 g, 0.75 mmole) and 2-dimethylaminoethylchloride hydrochloride (1.5 g, 0.011 mole), an oily product (0.2 g) was obtained, which was converted into the hydrochloride, m.p. 165-167°C.

^{1}H NMR (ppm, $CDCl_3$): 2.98 (s, 6H); 3.35 (m, 2H); 4.2 (m, 2H); 4.87 (s, 2H); 7.29-7.68 (m, 8H); 12.55 (s, 1H).

Example 33

4-[2-(11-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine hydrochloride

By the reaction of alcohol **7** (0.2 g, 0.61 mmole) and 4-(2-chloroethyl)-morpholine hydrochloride (1.9 g, 0.01 mole), an oily product (0.21 g) was obtained, which was converted into the hydrochloride, m.p. 190°C.

^{1}H NMR (ppm, $CDCl_3$): 3.08 (m, 2H); 3.32 (m, 2H); 3.63 (m, 2H); 4.05 (m, 2H); 4.25 (m, 4H); 4.87 (s, 2H); 7.29-7,69 (m, 8H); 13.25 (s, 1H).

Example 34

1-[2-(11-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride

By the reaction of alcohol **7** (0.2 g, 0.61 mmole) and 1-(2-chloroethyl)-piperidine monohydrochloride (1.9 g, 0.01 mole), an oily product (0.43 g) was obtained, which was converted into the hydrochloride, m.p. 184-185°C.

^{1}H NMR (ppm, $CDCl_3$): 1.51 (m, 3H); 2.23 (m, 7H); 3.07 (m, 2H); 3.18 (m, 2H); 4.23 (m, 2H); 7.32-7.74 (m, 8H); 12.3 (s, 1H).

Example 35

1-[2-(11-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride

By the reaction of alcohol **7** (0.2 g, 0.61 mmole) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (1.8 g, 0.01 mole), an oily product (0.27 g) was obtained, which was converted into the hydrochloride, m.p. 238°C.

^{1}H NMR (ppm, $CDCl_3$): 2.14 (m, 2H); 2.29 (m, 2H); 3.01 (m, 2H); 3.38 (m, 2H); 3.93 (m, 2H); 4.25 (m, 2H); 4.88 (s, 2H); 7.28-7.69 (m, 8H); 12.7 (s, 1H).

The compounds described in Examples 36-40 were prepared from alcohol **8** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 36.

Example 36

[3-(11-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride

To a solution of 3-dimethylaminopropylchloride hydrochloride (1.7 g, 0.011 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.15 g) and a toluene solution of alcohol **8** (0.23 g, 0.61 mmole) were added. The reaction mixture was heated under vigorous stirring and reflux for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product (0.25 g) was isolated, which was converted into the hydrochloride, m.p. 170-176°C.

^{1}H NMR (ppm, $CDCl_3$): 2.28 (m, 2H); 2.88 (d, 6H); 3.25 (m, 2H); 3.79 (m, 2H); 4.81 (s, 2H); 7.28-7.71 (m, 8H); 12.5 (s, 1H).

Example 37

[2-(11-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride

By the reaction of alcohol **8** (0.23 g, 0.61 mmole) and 2-dimethylaminoethylchloride hydrochloride (1.5 g, 0.01 mole), an oily product (0.31 g) was obtained, which was converted into the hydrochloride, m.p. 147-150°C.

^{1}H NMR (ppm, $CDCl_3$): 2.22 (s, 6H); 2.97 (m, 2H); 4.22 (m, 2H); 4.86 (s, 2H); 7.28-7.72 (m, 8H); 12.25 (s, 1H).

Example 38

4-[2-(11-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine

By the reaction of alcohol **8** (0.23 g, 0.61 mmole) and 4-(2-chloroethyl)-morpholine hydrochloride (2.2 g, 0.012 mole), an oily product (0.11 g) was obtained.

Example 39

1-[2-(11-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine

By the reaction of alcohol **8** (0.23 g, 0.61 mmole) and 1-(2-chloroethyl)-piperidine monohydrochloride (2.2 g, 0.012 mole), an oily product (0.09 g) was obtained.

Example 40

1-[2-(11-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine

By the reaction of alcohol **8** (0.23 g, 0.61 mmole) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (2.2 g, 0.012 mole), an oily product (0.17 g) was obtained.

^{1}H NMR (ppm, $CDCl_3$): 2.02 (m, 4H); 3.05 (m, 6H); 3.96 (m, 2H); 4.81 (s, 2H), 7.23-7.76 (m, 8H).

The compounds described in Examples 41-45 were prepared from alcohol **9** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 41.

Example 41

[3-(10-trifluoromethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine

To a solution of 3-dimethylaminopropylchloride hydrochloride (1.1 g, 0.007 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.15 g) and a toluene solution of alcohol **9** (0.18 g, 0.5 mmole) were added. The reaction mixture was heated under vigorous stirring and reflux for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product (0.11 g) was isolated.

^{1}H NMR (ppm, $CDCl_3$): 2.21 (m, 2H); 2.48 (s, 6H); 2.71 (m, 2H); 3.69 (t, 2H); 4.76 (s, 2H), 7.23-7.89 (m, 8H).

Example 42

Dimethyl-[2-(10-trifluoromethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-amine hydrochloride

By the reaction of alcohol **9** (0.18 g, 0.5 mmole) and 2-dimethylaminoethylchloride hydrochloride (1 g, 0.007 mole), an oily product was obtained, which was converted into the hydrochloride (0.1 g).

^{1}H NMR (ppm, $CDCl_3$): 2.94 (s, 6H); 3.32 (m, 2H); 4.18 (m, 2H); 4.85 (s, 2H); 7.29-7.70 (m, 7H); 7.93 (s, 1H); 12.85 (s, 1H).

Example 43

4-[2-(10-trifluoromethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine

By the reaction of alcohol **9** (0.18 g, 0.5 mmole) and 4-(2-chloroethyl)-morpholine hydrochloride (1.3 g, 0.007 mole), an oily product (0.20 g) was obtained.

^{1}H NMR (ppm, $CDCl_3$): 2.55 (m, 7H); 3.58 (m, 2H); 3.74 (m, 3H); 4.79 (s, 2H); 7.24-7.90 (m, 8H).

Example 44

1-[2-(10-trifluoromethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidin hydrochloride

By the reaction of alcohol **9** (0.18 g, 0.5 mmole) and 1-(2-chloroethyl)-piperidine monohydrochloride (1.3 g, 0.007 mole), an oily product (0.18 g) was obtained, which was converted into the hydrochloride.

^{1}H NMR (ppm, $CDCl_3$): 1.85 (m, 2H); 2.75-3.17 (m, 6H); 3.23 (m, 2H); 3.88 (m, 4H); 4.81 (s, 2H); 7.25-7.90 (m, 8H); 12.3 (s, 1H).

Example 45

1-[2-(10-trifluoromethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride

By the reaction of alcohol **9** (0.18 g, 0.5 mmole) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (1.2 g, 0.007 mole), an oily product (0.1 g) was obtained, which was converted into the hydrochloride.

^{1}H NMR (ppm, $CDCl_3$): 2.01 (m, 2H); 2.75 (m, 2H); 3.10 (m, 4H); 3.99 (m, 2H), 4.17 (m, 2H); 4.83 (s, 2H); 7.26-7.91 (m, 8H); 12.3 (s, 1H).

The compounds described in Examples 46-49 were prepared from alcohol **10** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 46.

Example 46

[3-(10-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine

To a solution of 3-dimethylaminopropylchloride hydrochloride (1.1 g, 0.007 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.15 g) and a toluene solution of alcohol **10** (0.16 g, 0.48 mmole) were added. The reaction mixture was heated under vigorous stirring and reflux for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product (0.17 g) was isolated.

^{1}H NMR (ppm, $CDCl_3$): 1.91 (m, 2H); 2.36 (s, 6H); 2.56 (m, 2H), 3.69 (t, 2H); 4.74 (s, 2H); 7.2-7.7 (m, 8H).

Example 47

[2-(10-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride

By the reaction of alcohol **10** (0.16 g, 0.48 mmole) and 2-dimethylaminoethylchloride hydrochloride (0.98 g, 0.0068 mole), an oily product was obtained, which was converted into the hydrochloride (0.12 g).

^{1}H NMR (ppm, $CDCl_3$): 2.36 (s, 6H); 2.65 (m, 2H); 3.73 (m, 2H); 4.78 (s, 2H); 7.2-7.7 (m, 8H); 7.93 (s, 1H).

Example 48

1-[2-(10-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride

By the reaction of alcohol **10** (0.16 g, 0.48 mmole) and 1-(2-chloroethyl)-piperidine monohydrochloride (1.25 g, 0.0067 mole), an oily product (0.11 g) was obtained, which was converted into the hydrochloride.

^{1}H NMR (ppm, $CDCl_3$): 1.57 (m, 2H); 2.95-3.87 (m, 10H); 4.78 (s, 2H); 7.2-7. (m, 8H).

Example 49

1-[2-(10-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine

By the reaction of alcohol **10** (0.16 g, 0.48 mmole) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (1.15 g, 0.0067 mole), an oily product (0.14 g) was obtained.

^{1}H NMR (ppm, $CDCl_3$): 1.87 (m, 4H); 2.76 (m, 4H); 2.88 (m, 2H); 3.86 (m, 2H); 4.78 (s, 2H); 7.2-7.65 (m, 8H).

The compounds described in Examples 50-54 were prepared from alcohol **11** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 50.

Example 50

[3-(10-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride

To a solution of 3-dimethylaminopropylchloride hydrochloride (1.18 g, 0.0074 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.15 g) and a

toluene solution of alcohol **11** (0.2 g, 0.53 mmole) were added. The reaction mixture was heated under vigorous stirring and reflux for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product (0.17 g) was isolated, which was converted into the hydrochloride.

^{1}H NMR (ppm, $CDCl_3$): 2.23 (m, 2H); 2.81 (d, 6H); 3.17 (m, 2H); 3.74 (m, 2H), 4.75 (s, 2H); 7.21-7.81 (m, 8H); 12.3 (s, 1H).

Example 51

[2-(10-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride

By the reaction of alcohol **11** (0.2 g, 0.53 mmole) and 2-dimethylaminoethylchloride hydrochloride (1.18 g, 0.0074 mole), an oily product was obtained, which was converted into the hydrochloride (0.12 g).

^{1}H NMR (ppm, $CDCl_3$): 2.91 (m, 6H); 3.27 (m, 2H); 4.15 (m, 2H); 4.80 (s, 2H); 7.23-7.84 (m, 8H); 12.4 (s, 1H).

Example 52

1-[2-(10-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride

By the reaction of alcohol **11** (0.2 g, 0.53 mmole) and 1-(2-chloroethyl)-piperidine monohydrochloride (1.27 g, 0.0074 mole), an oily product (0.15 g) was obtained, which was converted into the hydrochloride.

^{1}H NMR ($CDCl_3$): 1.38 (m, 2H); 1.85 (m, 2H); 2.17-2.36 (m, 2H); 2.76 (m, 2H), 3.12 (m, 2H); 3.17 (m, 2H); 4.18 (m, 2H); 4.78 (s, 2H); 7.25-7.90 (m, 8H); 12.3 (s, 1H).

Example 53

1-[2-(10-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine

By the reaction of alcohol **11** (0.2 g, 0.53 mmole) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (1.37 g, 0.0074 mole), an oily product (0.09 g) was obtained.

^{1}H NMR ($CDCl_3$): 1.69 (m, 4H); 2.62 (m, 4H); 2.69 (m, 2H); 3.81 (m, 2H); 4.78 (s, 2H); 7.22-7.85 (m, 8H).

Example 54

[2-(10-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride

By the reaction of alcohol **11** (0.2 g, 0.53 mmole) and 1-dimethylamino-2-propylchloride hydrochloride (1.18 g, 0.0074 mole), an oily product (0.12 g) was obtained, which was converted into the hydrochloride.

^{1}H NMR (ppm, $CDCl_3$): 1.17 (d, 3H); 2.47 (s, 6H); 3.02 (m, 1H); 3.68 (m, 2H); 4.77 (s, 2H); 7.1-7.85 (m, 8H).

The compounds described in Examples 55-57 were prepared from alcohol **12** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 55.

Example 55

[3-(9,11-dimethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride

To a solution of 3-dimethylaminopropylchloride hydrochloride (1.23 g, 0.0077 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.15 g) and a toluene solution of alcohol **12** (0.18 g, 0.55 mmole) were added. The reaction mixture

was heated under vigorous stirring and reflux for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product (0.13 g) was isolated, which was converted into the hydrochloride.

^{1}H NMR (ppm, $CDCl_3$): 2.22 (m, 2H); 2.29 (s, 3H); 2.61 (s, 3H); 2.81 (s, 6H); 3.17 (m, 2H); 3.74 (m, 2H); 4.75 (s, 2H); 7.11-7.67 (m, 7H); 12.3 (s, 1H).

Example 56

[2-(9,11-dimethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride

By the reaction of alcohol **12** (0.18 g, 0.55 mmole) and 2-dimethylaminoethylchloride hydrochloride (1.12 g, 0.0077 mole), an oily product was obtained, which was converted into the hydrochloride (0.09 g).

^{1}H NMR (ppm, $CDCl_3$): 2.29 (s, 3H); 2.61 (s, 3H); 2.91 (m, 6H); 3.28 (m, 2H); 4.13 (m, 2H); 4.80 (s, 2H); 7.12-7.67 (m, 7H); 12.3 (s, 1H).

Example 57

1-[2-(9,11-dimethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride

By the reaction of alcohol **12** (0.18 g, 0.55 mmole) and 1-(2-chloroethyl)pyrrolidine hydrochloride (1.32 g, 0.0077 mole), an oily product (0.11 g) was obtained.

^{1}H NMR (ppm, $CDCl_3$): 2.07 (m, 2H); 2.24 (m, 2H); 2.69 (m, 2H); 2.29 (s, 3H), 2.61 (s, 3H); 2.95 (m, 2H); 3.31 (m, 2H); 3.85 (m, 2H); 4.12 (m, 2H); 4.80 (s, 2H); 7.22-7.85 (m, 7H); 12.5 (s, 2H).

The compounds described in Examples 58-62 were prepared from alcohol **13** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 58.

Example 58

[3-(10,11-dichloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride

To a solution of 3-dimethylaminopropylchloride hydrochloride (1.5 g, 0.0095 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.15 g) and a toluene solution of alcohol **13** (0.2 g, 0.68 mmole) were added. The reaction mixture was heated under vigorous stirring and reflux for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product was isolated, which was converted into the hydrochloride (0.075 g).

^{1}H NMR (ppm, $CDCl_3$): 2.25 (m, 2H); 2.83 (s, 6H); 3.19 (m, 2H); 3.75 (m, 2H); 4.76 (s, 2H); 7.22-7.74 (m, 7H); 12.35 (s, 1H).

Example 59

[2-(10,11-dichloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride

By the reaction of alcohol **13** (0.2 g, 0.68 mmole) and 2-dimethylaminoethylchloride hydrochloride (1.4 g, 0.0095 mole), an oily product was obtained, which was converted into the hydrochloride (0.08 g).

^{1}H NMR (ppm, $CDCl_3$): 2.97 (s, 6H); 3.47 (m, 2H); 4.15 (m, 2H); 4.81 (s, 2H); 7.23-7.74 (m, 7H); 12.3 (s, 1H).

Example 60

4-[2-(10,11-dichloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine hydrochloride

By the reaction of alcohol **13** (0.2 g, 0.68 mmole) and 4-(2-chloroethyl)-morpholine hydrochloride (1.7 g, 0.0095 mole), an oily product was obtained, which was converted into the hydrochloride (0.11 g).

^{1}H NMR (ppm, $CDCl_3$): 3.02 (m, 2H); 3.27 (m, 2H); 3.60 (m, 2H); 3.99 (m, 2H); 4.16-4.36 (m, 4H); 4.80 (s, 2H); 7.22-7.74 (m, 7H); 12.55 (s, 1H).

Example 61

1-[2-(10,11-dichloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride

By the reaction of alcohol **13** (0.2 g, 0.68 mmole) and 1-(2-chloroethyl)-piperidine monohydrochloride (1.7 g, 0.0095 mole), an oily product was obtained, which was converted into the hydrochloride (0.045 g).

^{1}H NMR (ppm, $CDCl_3$): 1.42 (m, 2H); 1.87 (m, 2H); 2.23-2.37 (m, 2H); 2.78 (m, 2H); 3.22 (m, 2H); 3.65 (m, 2H); 4.19 (m, 2H); 4.79 (s, 2H); 7.22-7.74 (m, 7H); 12.1 (s, 1H).

Example 62

1-[2-(10,11-dichloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride

By the reaction of alcohol **13** (0.2 g, 0.68 mmole) and 1-(2-chloroethyl)-pyrrolidine hydrochloride (1.62 g, 0.0095 mole), an oily product was obtained, which was converted into the hydrochloride (0.09 g).

^{1}H NMR (ppm, $CDCl_3$): 2.02-2.25 (m, 4H); 2.94 (m, 2H); 3.32 (m, 2H); 3.88 (m, 2H); 4.15 (m, 2H); 4.81 (s, 2H); 7.22-7.73 (m, 7H); 12.4 (s, 1H).

The compounds described in Examples 63-64 were prepared from alcohol **14** and the corresponding chloroalkyldialkylamine hydrochloride according to the process described in Example 63.

Example 63

[3-(9-chloro-11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride

To a solution of 3-dimethylaminopropylchloride hydrochloride (1.22 g, 0.0077 mole) in 50% sodium hydroxide (5 ml), benzyltriethylammonium chloride (0.15 g) and a toluene solution of alcohol **14** (0.19 g, 0.55 mmole) were added. The reaction mixture was heated under vigorous stirring and reflux for 3 hours. Then it was cooled to room temperature, diluted with water and extracted with dichloromethane. After purification by column chromatography an oily product was isolated, which was converted into the hydrochloride (0.095 g).

^{1}H NMR (ppm, $CDCl_3$): 2.24 (m, 2H); 2.82 (s, 6H); 3.18 (m, 2H); 3.74 (m, 2H); 4.77 (s, 2H); 7.11-7.73 (m, 7H); 12.35 (s, 1H).

Example 64

[2-(9-chloro-11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride

By the reaction of alcohol **14** (0.19 g, 0.55 mmole) and 2-dimethylaminoethylchloride hydrochloride (1.12 g, 0.0077 mole), an oily product was obtained, which was converted into the hydrochloride (0.07 g).

^{1}H NMR (ppm, $CDCl_3$): 2.97 (m, 6H); 3.37 (m, 2H), 4.2 (m, 2H); 4.87 (s, 2H); 7.08-7.79 (m, 7H); 12.5 (s, 1H).

Example B

Preparation of aldehydes

To a dichloromethane solution of alcohol (0.002 mole/15 ml) (Table 1) dipyridine chrome (VI) oxide (pyridyl-dichromate, PDC, 0.003 mole) was added. The reaction mixture was stirred at room temperature within a period of 3 to18 hours. To the reaction mixture diethyl ether (20 ml) was added and the diluted reaction mixture was purified on a florisil column. The obtained product was additionally purified on a silica gel column.

According to the process of Example B, starting from appropriate alcohols (Table 1, compounds 4 and 3) there were obtained dibenzoazulene derivatives, wherein R_1, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 = H, R_{10} = CHO and R_2, R_3, R_4 and X have the meanings shown in Table 2.

Table 2

Comp.	X	R_2	R_3	R_4	m.p.(°C)	^{1}H NMR (ppm, $CDCl_3$)
15	O	F	H	H	-	7.07-7.52(m, 7H); 7.98 (s, 1H); 9.98 (s, 2H)
16	O	Cl	H	H	-	7.16-7.60(m, 7H); 8.01 (s, 1H); 9.99 (s, 2H)

The following compounds described in Examples 65-68 were prepared from aldehydes disclosed in Table 2 and the corresponding phosphorous-ylides according to the process described in Example 65.

Example 65

3-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-yl)-acrylic acid methyl ester

To a solution of aldehyde **15** (0.07 g, 0.0024 mole) in toluene (10 ml), ylide **III** (methyl(triphenyl)phosphoranylide acetate) (0.08 g, 0.0024 mole) was added. The reaction mixture was stirred under reflux for 4 hours and then it was cooled to room temperature, evaporated to dryness and extracted with ethyl acetate. After purification by column chromatography a crystalline product (0.03 g) was isolated.

^{1}H NMR (ppm, $CDCl_3$): 3.82 (s, 3H); 6.31 (d, 1H, J=15.67 Hz); 7.01-7.07 (m, 2H); 7.12-7.17 (m, 1H); 7.21-7.46 (m, 4H); 7.48 (s, 1H); 7.80 (d, 1H, J=15.69 Hz).

Example 66

3-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-yl)-acrylic acid methyl ester

To a solution of aldehyde **16** (0.15 g, 0.48 mmole) in tetrahydrofuran (20 ml), ylide **III** (0.24 g, 0.72 mmole) was added. The reaction mixture was stirred under reflux for 4 hours and then it was cooled to room temperature, evaporated to dryness and extracted with ethyl acetate. After purification by column chromatography a crystalline product (0.08 g) was isolated.

^{1}H NMR (ppm, $CDCl_3$): 3.82 (s, 3H); 6.30 (d, 1H, J=15.68 Hz); 7.08-7.57 (m, 8H); 7.80 (d, 1H, J=15.68 Hz).

Example 67

4-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-yl)-but-3-ene-2-one

To a solution of aldehyde **15** (0.14 g, 0.47 mmole) in toluene (10 ml), ylide **IV** (acetylmethylentriphenylphosphoran) (0.15 g, 0.47 mmole) was added. The reaction mixture was stirred under reflux for 4 hours and then it was cooled to room temperature, evaporated to dryness and extracted with ethyl acetate. After purification by column chromatography a crystalline product (0.08 g) was isolated.

^{1}H NMR (ppm, $CDCl_3$): 2.35 (s, 3H); 6.60 (d, 1H, J=15.85 Hz); 7.02-7.08 (m, 2H); 7.14-7.17 (m, 1H); 7.22-7.48 (m, 4H); 7.52 (s, 1H); 7.65 (d, 1H, J=15.86 Hz).

Example 68

4-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-yl)-but-3-ene-2-one

To a solution of aldehyde **16** (0.15 g, 0.48 mmole) in tetrahydrofuran (10 ml), ylide **IV** (0.15 g, 0.47 mmole) was added. The reaction mixture was stirred under reflux for 4 hours and then it was cooled to room temperature, evaporated to dryness and extracted with ethyl acetate. After purification by column chromatography a crystalline product (0.08 g) was isolated.

^{1}H NMR (ppm, $CDCl_3$): 2.39 (s, 3H); 6.61 (d, 1H, J=15.87 Hz); 7.01-7.60 (m, 8H); 7.65 (d, 1H, J=15.86 Hz).

Example 69

3-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-yl)-acrylic acid

The hydrolysis of the ester prepared as described in Example 65 (0.03 g, 0.085 mmole) was performed with 2 M KOH (reflux, 2 to 5 hours) and by acidifying the reaction mixture with concentrated HCl. The obtained crystalline product was filtered off and washed with water (0.02 g).

^{1}H NMR (ppm, $CDCl_3$): 6.3 (d, 1H); 7.02-7.09 (m, 2H); 7.12-7.17 (m, 1H); 7.22-7.48 (m, 4H); 7.53 (s, 1H); 7.9 (d, 1H).

Example 70

3-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-yl)-propionic acid

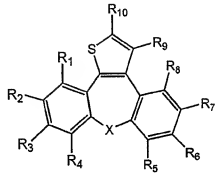
To an ethanol solution (10 ml) of the acid prepared in Example 66, 5% Pd/C (5 mg) moistened with water (50%) was added. The reaction mixture was stirred at room

temperature in hydrogen atmosphere at the pressure of 300 kPa. After the filtration of the catalyst and the evaporation of the solvent a product was obtained, which was purified by column chromatography on a silica gel column.

^{1}H NMR ($CDCl_3$): 2.83 (t, 2H); 3.23 (t, 2H); 6.93-7.45 (m, 7H).

CLAIMS

1. Dibenzoazulene derivatives, their pharmacologically acceptable salts and solvates represented by formula I



I

characterized in that

X can represent CH_2 or a heteroatom such as O, S, S(=O), $S(=O)_2$ or NR_{13}, wherein R_{13} means hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, arylcarbonyl, C_{1-6} alkylsulfonyl or arylsulfonyl and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 independently from each other represent substituents, which can be hydrogen, halogens (fluorine, chlorine or bromine); or C_1-C_7 alkyls, alkenyls, aryls or heteroaryls; or can represent different groups: halomethyl, hydroxy, C_1-C_7 alkoxy or aryloxy, C_1-C_7 alkylthio or arylthio, C_1-C_7 alkylsulfonyl, ciano, amino, mono- and di-C_1-C_7 substituted amines, derivatives of carboxylic group (C_1-C_7 carboxylic acids and their anhydrides, C_1-C_7 unsubstituted, mono-, di-substituted amides, C_1-C_7 alkyl or aryl esters), C_1-C_7 derivatives of carbonyl group (C_1-C_7 alkyl or aryl carbonyls), and R_{10} can represent substituents such as: C_2-C_{15} alkyls, C_2-C_{15} alkenyls, C_2-C_{15} alkinyls, aryls or heteroaryls, C_1-C_{15} haloalkyls, C_1-C_{15} hydroxyalkyls, C_1-C_{15} alkyloxy, C_1-C_{15} alkylthio, C_3-C_{15} alkylcarbonyls, C_2-C_{15} alkylcarboxylic acid, C_2-C_{15} alkylsters, C_1-C_{15} alkylsulfonyls, C_1-C_{15} alkylarylsulfonyls, arysulfonyls and C_1-C_{15} alkylamines represented by the general formula

$-(CH_2)_n-A$

wherein

n means 1-15, and

one or more methylene groups that can be substituted with an oxygen or sulfur atom, and

A represents a five- or six-membered, saturated or unsaturated ring with one, two or three heteroatoms, or

wherein R_{11} and R_{12} independently from each other represent hydrogen, C_1-C_7 alkyl, alkenyl, alkinyl, aryl or heteroaryl, or a heterocycle with 1-3 heteroatoms.

2. A compound and salt according to claim 1, characterized in that X represents -S- or -O-.

3. A compound and salt according to claim 2, characterized in that R_{10} represents $-CH_2O(CH_2)_n-A$.

4. A compound and salt according to claim 3, characterized in that A represents morpholine-4-yl.

5. A compound and salt according to claim 3, characterized in that A represents piperidine-1-yl.

6. A compound and salt according to claim 3, characterized in that A represents pyrrolidine-1-yl.

7. A compound and salt according to claim 3, characterized in that A represents

8. A compound and salt according to claim 7, characterized in that R_{11} and R_{12} simultaneously represent $-CH_3$ or $-CH_2CH_3$.

9. A compound and salt according to claim 2, characterized in that R_{10} represents $-CH_2OH$.

10. A compound and salt according to claim 2, characterized in that R_{10} represents -CHO.

11. A compound and salt according to claim 2, characterized in that R_{10} represents $-CH=CH(CH_2)_nCOOR_{13}$, wherein n can be from 0 to 12 and R_{13} has a meaning as previously defined.

12. A compound and salt according to claim 2, characterized in that R_{10} represents $-(CH_2)_nCOOR_{13}$, wherein n can be from 0 to 13 and R_{13} has a meaning as previously defined.

13. A compound and salt according to claim 11, characterized in that n is 0 and R_{13} is -H or $-CH_3$.

14. A compound and salt according to claims 2-9, characterized in that R_2 is F, Cl, Br or $-CH_3$.

15. A compound and salt according to claims 2-9, characterized in that R_3 is F, Cl, Br, $-CF_3$ or $-CH_3$.

16. A compound and salt according to claims 2-9, characterized in that R_4 is F, Cl or $-CH_3$.

17. Process for the preparation of dibenzoazulene derivatives represented by the formula (ii), wherein all radicals and symbols have the meanings as defined in claim 9,

characterized in that a hydride reduction of an ester of the formula (i), wherein all radicals and symbols have the previously defined meanings, is performed in suitable nonpolar solvents (preferably aliphatic ethers) at a temperature from 0 to 60°C within a period of 1 to 5 hours, whereupon an isolation and purification of the thus obtained alcohol compounds by recrystallization or column chromatography can be performed.

18. Process for the preparation of dibenzoazulenes represented by the formula (iii), wherein all radicals and symbols have the meanings as defined in claim 10, characterized in that alcohols of general formula **I**, wherein all radicals and symbols have the meanings as defined in claim 9, are subjected to an oxidation with pyridinyl-dichromate or pyridinyl-chlorochromate, the reaction in dichloromethane being performed at room temperature within a period of 1 to 2 hours, whereupon an isolation and purification of the thus obtained aldehyde compounds can be performed by column chromatography.

19. A process for the preparation of a compound of the general formula **I**, wherein all radicals and symbols have the meanings as defined in claim 3, characterized in that an alcohol of the formula (ii), wherein all radicals and symbols have meanings as defined in claim 9, is reacted with a compound of the formula **II**

$$Cl\text{-}(CH_2)_n\text{-}A \quad \textbf{II}$$

wherein symbols n and A have meanings as previously defined, the reaction being performed at a temperature from 20 to 100°C within a period of 1 to 24 hours under the conditions of phase-transfer catalysis in a two-phase alkaline medium (preferably 50% NaOH-toluene) and in the presence of a phase-transfer catalyst (preferably benzyl-triethyl-ammonium-chloride, benzyl-triethyl-ammonium-bromide, cetyl-trimethyl-bromide), and after the treatment of the reaction mixture the obtained product is isolated by recrystallization or chromatography on a silica gel column.

20. A process for the preparation of a compound of a formula **I**, wherein all radicals and symbols have the meanings as defined in claim 11, characterized in that an aldehyde of a general formula (iii), wherein all radicals and symbols have the meanings as defined in claim 10, is reacted with a triphenylphosphorous reagent of the formula **III**

$$Ph_3P^+CH^-(CH)_2)_nCOOCH_3 \quad \textbf{III}$$

the reaction being performed in a suitable dry solvent at reflux temperature of the solvent within a period of 1 to 24 hours, and after the treatment of the reaction mixture the obtained ester is isolated, purified by recrystallization or chromatography on silica gel column and hydrolyzed by refluxing in 20% KOH for a period of 3 hours and then the product is isolated by acidifying with HCl and filtration.

21. A process for the preparation of a compound of the general formula **I**, wherein all radicals and symbols have the meanings as defined in claim 1, characterized in that an aldehyde of the general formula **I**, wherein all radicals and symbols have the meanings as defined in claim 10, is reacted with a triphenylphosphorous reagent of the formula **IV**

$$Ph_3P^+CH^-(CH)_2)_nCOCH_3 \quad \textbf{IV}$$

the reaction being performed in a suitable dry solvent at reflux temperature of the solvent within a period of 1 to 24 hours, and after the treatment of the reaction mixture the obtained methyl ketone is isolated and purified by recrystallization or chromatography on a silica gel column.

22. A process for the preparation of a compound of the general formula **I**, wherein all radicals and symbols have meanings as defined in claim 12, characterized in that an alkene compound defined in claim 11, wherein all radicals and symbols have the meanings as defined in claim 11, is subjected to catalytic hydrogenation in the presence of a catalyst that may be paladium on active charcoal, rhodium or platinum (IV) oxide in a suitable organic solvent under a hydrogen pressure of 100 kPa to 300

kPa within a period of 2 to 6 hours and then the product is purified by chromatography on a siliea gel column.

23. Compounds:
dimethyl-[3-(8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-amine hydrochloride,
dimethyl-[2-(8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-amine hydrochloride,
4-[2-(8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine hydrochloride,
1-[2-(8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride,
1-[2-(8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride,
[3-(9-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine,
[2-(9-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine,
4-[2-(9-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine,
1-[2-(9-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine,
1-[2-(9-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine,
[3-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine,
[2-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine,
4-[2-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine,
1-[2-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine,
1-[2-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine,
[3-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride,
[2-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride,
4-[2-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine hydrochloride,

1-[2-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride,

1-[2-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride,

[3-(1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride,

[2-(1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride,

4-[2-(1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine hydrochloride,

1-[2-(1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride,

1-[2-(1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride,

[3-(11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride,

[2-(11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride,

4-[2-(11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine hydrochloride,

1-[2-(11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride,

1-[2-(11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride,

[3-(11-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride,

[2-(11-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride,

4-[2-(11-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine hydrochloride,

1-[2-(11-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride,

1-[2-(11-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride,

[3-(11-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride,

[2-(11-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride,

4-[2-(11-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine,

1-[2-(11-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine,

1-[2-(11-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine,

[3-(10-trifluoromethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine,

dimethyl-[2-(10-trifluoromethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-amine hydrochloride,

4-[2-(10-trifluoromethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine,

1-[2-(10-trifluoromethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride,

1-[2-(10-trifluoromethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride,

[3-(10-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine,

[2-(10-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride,

1-[2-(10-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride,

1-[2-(10-chloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine,

[3-(10-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride,

[2-(10-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride,

1-[2-(10-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride,

1-[2-(10-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine,

[2-(10-bromo-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride,
[3-(9,11-dimethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride,
[2-(9,11-dimethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride,
1-[2-(9,11-dimethyl-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride,
[3-(10,11-dichloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride,
[2-(10,11-dichloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride,
4-[2-(10,11-dichloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-morpholine hydrochloride,
1-[2-(10,11-dichloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-piperidine hydrochloride,
1-[2-(10,11-dichloro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-pyrrolidine hydrochloride,
[3-(9-chloro-11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-propyl]-dimethyl-amine hydrochloride,
[2-(9-chloro-11-fluoro-1,8-dithia-dibenzo[*e,h*]azulene-2-ylmethoxy)-ethyl]-dimethyl-amine hydrochloride,
3-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-yl)-acrylic acid methyl ester,
3-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-yl)-acrylic acid methyl ester,
4-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-yl)-but-3-ene-2-one,
4-(11-chloro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-yl)-but-3-ene-2-one,
3-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-yl)-acrylic acid,
3-(11-fluoro-8-oxa-1-thia-dibenzo[*e,h*]azulene-2-yl)-propionic acid.

24. Use of compounds according to claims 1 to 16 as inhibitors of production of cytokines or inflammation mediators in the treatment or prophylaxis of any

pathological condition or disease induced by excessive unregulated production of cytokines or inflammation mediators, whereat non-toxic doses of suitable pharmaceutical preparations can be administered orally, parenterally or topically.

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/HR 01/00027

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 A61K31/55 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 887 339 A (BOEHRINGER MANNHEIM GMBH) 30 December 1998 (1998-12-30) claims 1-4	1-24
X	P. CAGNIANT, G. KIRSCH: "Contribution à l'étude de la réaction de Vilsmeier-Haack dans le domaine des cétones tricycliques: dihydro-10.11 oxo-10-5H-dibenzo'a,d!cycloheptène, dihydro-10.11 oxo-10-dibenzo'b,f!oxépinne et dihydro-10.11 oxo-10-dibenzo'b,f!thiépinne. Synthèse de nouveaux composés hétéro-tétracycliques" C. R. HEBD. SEANCES ACAD. SCI., SER. C, vol. 283, no. 15, 1976, pages 683-686, XP001008270 cited in the application * Compounds of formula V *	1,2

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2001	01/08/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Herz, C

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/HR 01/00027

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 887339 A	30-12-1998	AU 8729298 A	19-01-1999
		WO 9900355 A	07-01-1999